REMARKS

Claims 1 and 36-63 are pending in this application. Support for the amended Claim 1 and new claims can be found throughout the specification and claims as filed.

The Invention

The present invention provides an apparatus for performing biological reactions on a substrate layer having a multiplicity of biomolecular probes, including oligonucleotides. In a preferred embodiment, the array comprises a 3-dimensional polyacrymide matrix for anchoring the binding probes. The array is optionally covered with a water soluble compound that is solid at one temperature and a liquid at another. The array is further covered with a flexible layer. This flexible layer permits mixing of the hybridization solution after the optional liquidization of the water soluble compound and detection of hybridization *in situ*, and further prevents evaporation of water from the small reaction volume contained between the flexible layer, a first surface of the substrate, and further enclosed by an adhesive layer that affixes the flexible layer to the first surface of the substrate. Fluid inlet and optional outlet ports in the chamber provide for control of fluid flow into and out of the chamber.

Drawings

Formal drawings will be filed later, with corrections made under 37 CFR 1.83(a).

Claims Objections

The Examiner has identified the incorrect numbering of the claims under 37 CFR 1.126. Cancellation of claims in question renders this issue moot. Accordingly, Applicants respectfully request withdrawal of the claim objections.

Rejection under the Double Patenting Doctrine

Claims 1-33 (corrected numbering) are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of copending Application No. 09/464490. Claim 34 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 33 of copending Application No. 09/464490. Claim 35 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 34 of copending Application No. 09/464490.

Claims 1-32 of copending Application No. 09/464490 are still pending, whereas claims 33 and 34 of copending Application No. 09/464490 have been allowed. Applicants respectfully request the Examiner consider the amended and new claims. If the Examiner determines that the double-patenting rejection of the amended and new claims is proper, Applicants will file terminal disclaimers against the claims in copending Application No. 09/464490.

Rejection under 35 U.S.C. § 112, 2d Paragraph

Claims 24 and 25 stand rejected under 35 U.S.C. § 112, 2d paragraph as the term "scanner" lacks antecedent basis. Claim 20 stands rejected under 35 U.S.C. § 112, 2d paragraph as the term "the resistive heater" lacks antecedent basis.

Applicants submit that the amended and new claims cure the above-identified problems of lacking antecedent basis. Accordingly, this rejection should be withdrawn.

Rejection under 35 U.S.C. § 102(e)

Claims 1-3, 8-12 and 16-18 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Besemer et al. (U.S. Patent No. 5, 945,337) (Besemer).

The present invention is discussed above.

Besemer teaches an apparatus and methods for packaging a chip. In particular, the packaging apparatus is a body, whether a single component or welded together from two components, with a cavity for mounting a chip. As the Examiner has noted, Besemer teaches that a substrate having an array of probes is attached to the cavity using an adhesive and that a cover can be mated to the package for sealing the cavity. As illustrated in Figures 27b in Besemer, Cover 2770 is mated to surface 2705 with an adhesive 2772, and the cavity itself provides the reaction volume for the substrate mounted therein. Notably, cover 2770 is preferably composed of materials such as glass, acrylic. Column 18, lines 2-4. Further, surface 2705 is distinct from the surface 2791 onto which chip 2790 is mated.

As the Examiner is aware, "[i]t is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

It is clear that the cover taught in Besemer is distinct from the flexible cover in the present invention. An ordinary meaning for "flexible" applies to something that can be folded or bent without breaking, which does not apply to glass or acrylic. Further, the reaction volume in the present invention is formed by a flexible layer and a first surface onto which an array of probes are positioned, and therefore is very distinct from the reaction volume formed by cavity as taught in Besemer. Therefore, Besemer anticipates neither the element of flexible layer nor the element of reaction volume in the present invention. Thus, independent Claims 1, 61, and 62 in the present invention are not anticipated by Besemer. Because they necessarily contain the elements of flexible layer and reaction volume formed by the flexible layer and the surface onto which the array of probes are positioned, the dependent claims 36-60 and 63 are not anticipated by Besemer either. Accordingly, Applicants respectfully submit that the pending claims are patentable over Besemer and request the rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 13-15 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Besemer in view of Van Antwerp et al. (U.S. Patent No. 5,786,439) (Van Antwerp).

Claims 4-7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Besemer in view of Mirzabekov et al. (U.S. Patent No. 5,905,024) (Mirzabekov).

Claims 22 & 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Besemer in view of Chavan et al. (U.S. Patent No. 6,109,113, August 29, 2000) (Chavan).

Claims 24-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Besemer in view of Phillips et al. (U.S. Patent No, 6,171,793, January 9, 2001) (Phillips).

Claims 19-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Besemer in view of Li et al. (U.S. Patent No. 5,960,014) (Li).

All of the rejected claims have been cancelled. Instead, Applicants respectfully submit that none of the pending claims is obvious over the references above or any combination thereof for the following reasons.

Besemer is discussed above. Also as noted above, Besemer neither teaches nor suggests a flexible layer or a reaction volume formed by the flexible layer and the surface onto which the array of probes is positioned.

Van Antwerp teaches coating a biosensor with a water *insoluble* hydrogel matrix. The insoluble matrix has a solid component with both hydrophillic and hydrophobic character, and a liquid component that is retained in the matrix by intermolecular forces. Column 3, lines 30–35. The function of this hydrogel is to maintain a uniform layer of water on any surface to which the hydrogel is applied. Van Antwerp neither teaches nor suggests a flexible layer or a reaction volume formed by the flexible layer and the surface onto which the array of probes is positioned.

Mirzabekov teaches a method of fractionating and sequencing DNA via affinity interactions. Additionally, Mirzabekov teaches the use of polyacrylamide gel matrices for constructing the probe arrays to be used in such fractionation and sequencing.

Mirzabekov neither teaches nor suggests a flexible layer or a reaction volume formed by the flexible layer and the surface onto which the array of probes is positioned.

Chavan teaches a capacitive pressure sensor that uses polysilicon as an electrostatic bonding medium and as a lead transfer to make an electrical connection to an electrode within a vacuum sealed chamber. Chavan neither teaches nor suggests a flexible layer or a reaction volume formed by the flexible layer and the surface onto which the array of probes is positioned.

Phillips teaches a method of obtaining data generated by gene probe arrays using a scanner. Phillips neither teaches nor suggests a flexible layer or a reaction volume formed by the flexible layer and the surface onto which the array of probes is positioned.

Li teaches a thin film resistor for optoelectronic integrated circuits. Li neither teaches nor suggests a flexible layer or a reaction volume formed by the flexible layer and the surface onto which the array of probes is positioned. Further, M.P.E.P. Section 2141.01(a) provides that "[i]n order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446, (Fed. Cir. 1992). Applicants respectfully submit that Li is neither in the field of the present invention nor "reasonably pertinent" to the present invention.

Assuming all the references cited above are analogous arts, the Examiner bears the burden of establishing a *prima facie* case of obviousness when rejecting claims under 35 U.S.C. §103. See, e.g., *In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. Section 2142.

To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not the Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. Section 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

It is clear that the references, whether alone or combined, cited by the Examiner, do not teach or suggest the claim limitation of a flexible layer or a reaction volume formed by the flexible layer and the surface onto which the array of probes is positioned.

With respect to the primary reference, Besemer, Applicants further submit that there is no motivation coming from the prior art references to modify the Besemer packaging device so that the cover would be a flexible layer and the reaction volume would be formed by the flexible layer and the surface onto which the chip was mounted. The essence of the Besemer invention lies in "packaging," that is, a device that holds and creates a reaction chamber for a chip mounted therein. The chip itself, i.e., a wafer–substrate–with numerous probe arrays on it (Column 4, lines 45-54), does not contribute to the reaction volume; within a packaging device without a chip mounted in it yet, the cavity "bounded by the mounting surface and the upper surface" still provides a reaction volume. In contrast, the substrate of

Therefore, Applicants respectfully submit that the pending claims are not obvious over Besemer alone or in combination of any other references cited above and request a withdrawal of this rejection.

Applicants submit that the pending claims are in form for immediate allowance and the Examiner is respectfully requested to early notification to that effect.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,

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Version with Markings to Show Changes Made

(Amended) 1. An apparatus for performing biological reactions, comprising:

(a) a substrate having a first surface and a second surface ~~opposite thereto~~;

(b) an array ~~a multiplicity~~ of biomolecul<u>ares</u> probes positioned on the first surface ~~of the substrate~~; and

(c) a flexible layer affixed to the first surface ~~of the substrate~~ by an adhesive layer, forming a reaction volume;

wherein said apparatus comprises at least a first port into said reaction volume.; ~~wherein the adhesive layer is deposited on the first surface of the substrate and encloses an area thereupon, and wherein a volume is enclosed between the flexible layer and the first substrate surface in the area defined by the adhesive layer; and~~

~~(d) first and second ports extending through the flexible layer and the adhesive layer into the volume enclosed between the flexible layer and the first substrate surface in the area defined by the adhesive layer.~~

Please cancel Claims 2-35.

New Claims:

36. An apparatus according to claim 1 wherein said biomolecular probes are oligonucleotides.

37. An apparatus according to claim 1 wherein said first port extends through said flexible layer.

38. An apparatus according to claim 1 wherein said first port extends from said second surface to said reaction volume.

39. An apparatus according to claim 1 wherein said substrate comprises glass.

40. An apparatus according to claim 1 wherein said substrate comprises a polymer.

41. An apparatus according to claim 1 wherein said substrate comprises ceramic.

42. An apparatus according to claim 1 wherein said substrate comprises silicon.

43. An apparatus according to claim 1 wherein said biomolecular probes are anchored to said first surface using polyacrylamide.

44. An apparatus according to claim 1 wherein said biomolecular probes are anchored to a continuous layer of polyacrylamide.

45. An apparatus according to claim 1 further comprising a heating element positioned under said reaction volume.

46. An apparatus according to claim 45 wherein said heating element is a resistive heater.

47. An apparatus according to claim 1 comprising a plurality of arrays of biomolecular probes, and said flexible layer, said adhesive layer and said first surface comprise a plurality of reaction volumes each containing one of said arrays.

48. An apparatus according to claim 1 wherein said flexible layer comprises plastic.

49. An apparatus according to claim 1 wherein said flexible layer comprises translucent plastic.

50. An apparatus according to claim 1 wherein said flexible layer comprises rubber.

51. An apparatus according to claim 1 wherein said flexible layer comprises polyester.

52. An apparatus according to claim 1 wherein said flexible layer comprises Teflon.

53. An apparatus according to claim 1 wherein said flexible layer comprises polypropylene.

54. An apparatus according to claim 1 wherein said flexible layer comprises polyethylene.

55. An apparatus according to claim 1 wherein said flexible layer comprises polyvinylidene chloride.

56. An apparatus according to claim 1 wherein said flexible layer is a gas permeable membrane.

56. An apparatus according to claim 1 wherein said reaction volume further comprises a water-soluble compound that is a solid at room temperature and a liquid at a second, higher temperature.

57. An apparatus according to claim 1 further comprising a scanner.

58. An apparatus according to claim 1 further comprising a sample preparation chip.

59. An apparatus according to claim 58 wherein said first port extends from said second surface to said reaction volume and said sample preparation chip is in contact with said second surface and wherein said sample preparation chip has a port that is aligned with said first port.

60. An apparatus according to claim 1 further comprising a roller, wherein said roller is in contact with said flexible layer.

61. A method of making an apparatus comprising:

a) providing a substrate with a first and a second surface, wherein said first surface comprises a continuous layer of derivatized polyacrylamide;

b) contacting said derivatized polyacrylamide with biomolecular probes;

c) forming an amide bond between said derivatized polyacrylamide and said biomolecular probe;

d) adding a flexible layer to said first surface to form a reaction volume.

62. A method of detecting the presence of a target molecule in a sample comprising:

a) providing an apparatus comprising:

i) a substrate comprising a first and a second surface;

ii) an array of biomolecular probes positioned on said first surface; and

iii) a flexible layer affixed to said first surface by an adhesive layer, forming a reaction volume; wherein said apparatus comprises at least a first port into said reaction volume;

b) introducing said sample through said first port into said reaction volume under conditions that allow the binding of said target molecule to at least one of said biomolecular probes; and

c) detecting said binding as an indication of the presence of said target molecule.

63. A method according to claim 62 wherein said target molecule is labeled with a fluorescent label.